

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61K 31/74, A01N 39/00</b>		A1	(11) International Publication Number: <b>WO 95/16454</b> (43) International Publication Date: 22 June 1995 (22.06.95)
(21) International Application Number: <b>PCT/US94/14536</b>		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).	
(22) International Filing Date: 15 December 1994 (15.12.94)			
(30) Priority Data: 169,843 17 December 1993 (17.12.93) US 250,248 27 May 1994 (27.05.94) US			
(71)(72) Applicant and Inventor: KLIGMAN, Albert, M. [US/US]; 210 W. Rittenhouse Square #3302, Philadelphia, PA 19103 (US).		Published <i>With international search report.</i>	
(74) Agents: SCHWARZE, William, W. et al.; Panitch Schwarze Jacobs & Nadel, P.C., 36th floor, 1601 Market Street, Philadelphia, PA 19103-2398 (US).			

**(54) Title:** METHOD FOR TREATMENT OF PAPULO-PUSTULES AND COMEDONES OF THE SKIN**(57) Abstract**

Papulo-pustules in the skin of patients suffering from various forms of acne, folliculitis and rosacea may be rapidly resolved by a spot therapy which involves topically applying to the exterior surface of the papulo-pustule (pimple) an aqueous solution containing hydrogen peroxide and preferably also at least one fruit acid and/or salicylic acid. A preferred fruit acid is glycolic acid. Both open and closed comedones are also effectively treated by spot therapy with the aqueous solution containing hydrogen peroxide, fruit acid and salicylic acid. The solution preferably contains 3 to 6 weight percent hydrogen peroxide, 2 to 4 weight percent glycolic acid and 2 to 4 weight percent salicylic acid, and is preferably applied 2 to 3 times daily. Treatments continue for 1 to 3 days when directed to papulo-pustules and 7 to 20 days when directed to comedones. The therapy also substantially reduces or avoids hyperpigmentation and scarring after resorption of the papulo-pustules. Application of the hydrogen peroxide solution to the earliest spot (lesion) prevents development of larger papulo-pustules and reduces the possibility of scarring and hyperpigmentation.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LJ	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

**METHOD FOR TREATMENT OF  
PAPULO-PUSTULES AND COMEDONES OF THE SKIN**

**Field of the Invention**

5           The present invention relates to the topical treatment of papulo-pustules (pimples) and comedones of the human face. More particularly, the invention is directed to a spot therapy for rapid drying up of the papulo-pustules, a method for reducing scarring and hyperpigmentation owing to  
10          more rapid resorption of the papulo-pustules, and to spot therapy for the treatment of comedones.

**Background of the Invention**

15          Papulo-pustules, commonly known as pimples or zits, are common lesions of the skin resulting from diseases, such as rosacea, folliculitis and various forms of acne, including particularly adolescent acne, post-adolescent female acne, peri-menopausal acne, acne cosmetica, acne detergicants, etc. A pustule is a soft pimple full of neutrophiles. It is yellow  
20          and can leak pus. Pustules are not infections, but are non-specific inflammatory reactions involving the disruption of the lining walls of the sebaceous follicles of the face. In acne, a pustule ensues when a comedo ruptures, dumping horn, bacteria, yeasts, hairs and sebum into the dermis.

25          This mix of toxicogenic materials creates a foreign body inflammatory response. Other pathogenic mechanisms involve a folliculitis of the lining epithelium which allows sebum to leak into the dermis, again provoking a neutrophilic response. This happens in rosacea, excessive soaping, and in  
30          response to pustulogenic chemicals in skin care products.

35          A papule is a deeper, larger inflammatory reaction which is more solid, but is still mainly made up of neutrophiles. A papule is more likely to scar and leave a pigmented spot. Papules are also quite common in blacks, who tend to react with greater inflammation to any trauma or chemical insult. Papules and pustules differ essentially only

- 2 -

in degree, and both types of lesions may be covered by the term "papulo-pustules" or more simply "pimples."

Papulo-pustules are obvious and spring up rapidly in less than 24 hours and even overnight. They may be quite sore and tender. These pimples take about 7-10 days to resorb or dry up without treatment. However, after resorption they may leave a long-lasting red spot in whites and in blacks a dark pigmented spot (hyperpigmentation) which may last for many months. This also happens in other dark-skinned persons, such as Orientals, and is considered to be a disquieting cosmetic defect.

Various methods have been tried in the past to dry up papulo-pustules, with varying degrees of success, but all with decided disadvantages. Freezing of the pimples with liquid nitrogen is helpful but requires a dermatologist to spray it on. A number of dermatologic formulations can help to clear pimples. The most venerable use is sulfurated materials, especially elemental sulfur, which may be dabbed onto the pimples. However, sulfur has an offensive odor and its yellow color makes it cosmetically unattractive.

Benzoyl peroxide is widely used to treat acne based on its antibacterial properties especially in suppressing P. acnes in follicles. It is applied to the entire face and is not used for spot therapy. However, its capacity to dry up existing pimples, even in 10 percent formulations, is very limited.

Glycolic acid is popular in many cosmetics and skin care treatments as a natural fruit acid. It is also a well-known exfoliant, widely used for light peels by dermatologists. Fruit acids, such as glycolic, citric or lactic, may be helpful as topical agents for spot therapy, but must be used at 40 percent peeling concentrations, usually in a physician's office. These are the so-called alpha-hydroxy acids which are currently the rage in women's magazines. At 50-75% concentrations, glycolic acid and other fruit acids are used by dermatologists to give a full face peel. Lactic and

- 3 -

glycolic acids at commercial OTC concentrations of 5-10 percent simply do not resolve pimples.

5 Salicylic acid is a standard keratolytic in OTC products to treat comedones, and is a well-known exfoliant widely used in light peels by dermatologists. Salicylic acid also has some anti-inflammatory effect and is often incorporated into topical drugs to reduce inflammation.

10 Finally, a variety of chemical irritants may have marginal effects on drying up pimples, but these are not spot therapies and are not well tolerated.

15 Prior treatments of acne which involve the use of hydrogen peroxide ( $H_2O_2$ ), for example U.S. patents 4,485,091 of Quinoderm Limited and 4,826,681 of L'Oreal, have not involved spot therapy of pimples, but rather treatment of the entire skin in an attempt to kill P. acnes, an organism which flourishes in comedones and which produces toxic products that lead to rupture of the follicular wall. Thus, P. acnes is a causative factor in acne. Inhibiting this organism is the objective for various antibacterial agents including 20 antibiotics and benzoyl peroxide.

Likewise, the Quinoderm patent is based upon killing P. acnes in the follicles using a cream, lotion or gel containing hydrogen peroxide and maintained at an acid pH. The L'Oreal patent involves an anhydrous solution of hydrogen peroxide applied to the entire face and specifically directed to killing P. acnes, the main organism in acne. However, the present invention has nothing to do with killing P. acnes.

#### Brief Summary of the Invention

30 According to the present invention, papulo-pustules may be rapidly resorbed by a spot therapy which comprises application to the exterior surface of the papulo-pustules of an aqueous solution comprising hydrogen peroxide and optionally at least one of a fruit acid and salicylic acid, in an amount, at a concentration and at a frequency sufficient to 35 effect resorption of the papulo-pustules within two to three

days. Preferably, the solution contains about 3 to 6 weight percent hydrogen peroxide, with or without a fruit acid such as glycolic acid and citric acid, present in a concentration equivalent to about 2 to 4 weight percent glycolic acid, and with or without 2 to 4 weight percent salicylic acid, and may be dabbed on the papulo-pustule in an amount sufficient to wet the surface 2 to 3 times daily for 1 to 3 days. The method of the invention is also effective to substantially lessen or avoid hyperpigmentation and scarring after resorption of the papulo-pustules.

Another aspect of the invention is a method for spot therapy of comedones, including both open and closed comedones, comprising topically applying to the exterior surface of the comedone an aqueous solution as described above containing hydrogen peroxide, a fruit acid and salicylic acid, said solution being applied in an amount, at a concentration and at a frequency sufficient to provide a comedolytic effect within about 7 to 20 days of therapy. Preferably, the solution may be dabbed on the comedone in an amount sufficient to wet the surface two or three times daily for about 10 to 20 days.

#### Detailed Description of the Preferred Embodiments

Hydrogen peroxide is a well known antiseptic and bleaching agent. It is an OTC product which can be purchased readily for disinfection and cleaning of wounds. It is generally safe and carries no risks. However, the present invention is not based upon a debridement, cleaning or disinfection action, but rather a resorption and drying up of the papulo-pustules.

Moreover, the present invention has nothing to do with the antibacterial effect of hydrogen peroxide. Thus, while hydrogen peroxide kills P. acnes in vitro, I have found it to be completely ineffective in vivo. For example, up to 10 weight percent aqueous solutions of hydrogen peroxide have been applied to skin with acne, but no reduction of the

- 5 -

follicular population of P. acnes has been found. In fact, even repeated applications do not limit the growth of this organism. The mode of action of hydrogen peroxide in this instance is entirely different. Hydrogen peroxide is not used in OTC preparations for acne. In contrast, benzoyl peroxide does suppress P. acnes *in vivo* and is commercially useful.

The oxidizing property of hydrogen peroxide is probably important in the mechanism of the present invention. After application to the skin, the site whitens and gets frothy, which is almost certainly due to the release of oxygen. The latter is a highly reactive chemical which combines quickly and avidly with skin proteins, resulting in their coagulation. This is the probable mechanism of whitening.

While concentrations of hydrogen peroxide in water up to about 10 percent by weight (w/v) have been found quite effective and act very quickly to resorb the papulo-pustules, such high concentrations are unnecessary and cause too much stinging and burning. Preferably, the concentration of hydrogen peroxide in water should be about 3-6 weight percent, and more preferably about 3-5 weight percent. This is a stable solution and requires no buffering.

According to a preferred embodiment of the present invention, hydrogen peroxide is co-formulated with one or more of the adjuvants salicylic acid and fruit acid, wherein exemplary fruit acids are glycolic acid, citric acid, lactic acid, malic acid, pyruvic acid and mixtures thereof. Glycolic acid is a preferred fruit acid. It is observed that said co-formulation affords benefits unavailable from the use of hydrogen peroxide alone. For example, the presence of one or more adjuvants serves to stabilize the hydrogen peroxide, and therefore provides a longer self-life to the composition. Also, the adjuvant(s) promote penetration of the composition into the tissue, and hence promote greater therapeutic effects.

Deep-seated papules and even cysts are more likely to respond to the co-formulation of the invention. It is also observed that the co-formulation promotes faster resorption of the papulo-pustules by, it is hypothesized, speeding up the drying effect of the hydrogen peroxide.

The co-formulation is more comedolytic than a formulation lacking the adjuvants of the invention: hydrogen peroxide alone has slight, if any, comedolytic effect. It is observed that when the composition of the invention is applied daily to large, ugly open comedones (also known as blackheads), the horny plugs fall out within 7 to 14 days. Closed comedones are also receptive to the inventive method, although the treatment typically takes longer, for example, up to about 20 days. The removal of comedones by spot therapy is a considerable improvement cosmetically. Elimination of comedones is prophylactic because all the inflammatory lesions in acne develop from the rupture of comedones.

The combination of hydrogen peroxide, fruit acid and salicylic acid can be applied to the entire face as a general treatment for acne, as well as to selected areas which tend to be more prone to infection.

Individual papulo-pustules on patients having multiple facial papulo-pustules were spot-treated with either the hydrogen peroxide containing co-formulations of the present invention, wherein the fruit acid was glycolic acid, or hydrogen peroxide unassociated with either glycolic or salicylic acid. It was convincingly shown that lesions subjected to the co-formulations of the instant invention generally responded more favorably, i.e., resorbed more quickly and without a residual mark.

In a preferred composition, the fruit acid is glycolic acid and it is present at a concentration of about 2 to 4 weight percent. When fruit acid(s) other than glycolic acid are present in the invention co-formulation, said fruit acid(s) should be present in an amount equivalent to about 2 to 4 weight percent glycolic acid. Combinations of glycolic

- 7 -

acid and one or more other fruit acids may also be used in the inventive co-formulations, where said combinations are present in a concentration equivalent to about 2 to 4 weight percent glycolic acid.

5 In preferred compositions, salicylic acid is present in a concentration of about 2 to 4 weight percent.

While higher adjuvant concentrations, for example above 5%, may be used, excessive peeling may result as well as chemical burns and irritation. Thus, it is preferred to keep 10 each adjuvant at a concentration below 5 weight percent. A composition having either glycolic acid or salicylic acid present in the range of about 2 to 4 weight percent is only a mild, tolerable irritant. Of course, where fruit acid(s) weaker or less effective than glycolic acid are used, 15 concentrations of such fruit acid may be higher than 5 weight percent.

Either fruit acid or salicylic acid may be used alone with the hydrogen peroxide, however preferably both adjuvants are co-formulated with hydrogen peroxide in order to 20 provide optimal stability and other desirable effects.

Glycolic acid is a preferred fruit acid. Salicylic acid and fruit acids, such as glycolic acid, are compatible with each other and with hydrogen peroxide, so that no special means are necessary in preparing the co-formulations.

25 Thickeners, such as methyl cellulose, or gelling agents can be added, if desired, to facilitate delivery to the skin.

The aqueous hydrogen peroxide solution with or without adjuvant may be simply applied in an amount sufficient 30 to wet the surface of the papulo-pustule. Since the pimple will immediately turn white upon application of the solution, the whitening is a good indicator of whether enough solution has been applied. That is, just enough need be applied to produce whitening of the pimple. However, an excess will do 35 no harm, and exactitude is not required.

Any appropriate means of application which will wet the surface of the papulo-pustule may be used. A cotton tipped rod or stick has been found suitable, and preferred would be a cotton or felt tipped applicator which could be carried around in a small vial in a purse or pocket, since frequent application is desirable.

The hydrogen peroxide solution with or without adjuvant should preferably be applied by dabbing or by other means on the papulo-pustules 2 to 3 times daily for 1 to 3 days, 2 to 3 days in the case of hydrogen peroxide alone. The pimples immediately turn white and then progressively dry up. The rapid resorption of the pimples is not only cosmetically useful, but also encourages compliance with the spot therapy treatment, since the patient sees the whitening and can perceive the drying process taking place.

The hydrogen peroxide solution of the invention with or without adjuvant can preferably be applied as soon as the first red spot appears, which patients readily recognize. However, fully developed papulo-pustules will also dry up quickly. One can treat 20-30 pimples at a time, but usually the patient will be treating many fewer than this. While pimples will resolve spontaneously over a period of a week or more without treatment, early application is important in order to lessen scarring and hyperpigmentation which follow tissue-destroying inflammatory reactions. Thus, the longer the pimple remains, the greater will be the hyperpigmentation and scarring.

Another feature of this invention is prophylaxis which rapidly converts the earliest detectable lesion, usually only a red, flat spot, into a small pustule. This can happen in as little as 1 to 2 hours. Continued applications bring about a rapid drying up of these diminutive, abortive pustules, thus reducing their sequelae. One may thus conceive of this spot therapy as a two-stage process: (1) rapid evolution into an abortive pimple and (2) rapid resorption. Application to the earliest lesions will prevent the

development of a larger papulo-pustule and reduce the possibility of scarring and hyperpigmentation.

5 Papulo-pustular acne is increasing in post-menopausal women, particularly as they compete in the marketplace. They need a convenient way to abort pimples and to look well groomed. The spot therapy of the present invention provides a convenient, swift and exact targeting of the problem pimples.

10 Another important use is in female blacks in whom every pimple leaves a deeply pigmented spot which lasts for months. Early treatment in blacks according to the present invention has been shown to dry up the lesions and greatly reduce the post-inflammatory hyperpigmentation, which is really a tattoo of melanin dumped into the dermis. The 15 treatment similarly reduces the sequela of red spots which follow pimples in whites.

20 While the treatments of the present invention are applicable to all types of papulo-pustules or pimples, they have been found to be particularly useful in the spot therapy of papulo-pustules in patients suffering from adolescent acne, post-adolescent female acne, peri-menopausal acne, acne 25 cosmetica and in rosacea. As a matter of fact, follicular pustules of whatever origin, including bacterial infections, will also resorb quickly when treated with the solution.

25 The treatments of the present invention using hydrogen peroxide in combination with the above adjuvants are also applicable to comedones, including both open and closed comedones. With spot therapy comprising topically applying to the exterior surface of a comedone an aqueous solution 30 containing hydrogen peroxide, fruit acid and salicylic acid according to the invention, a comedolytic effect is observed within 7 to 20 days of therapy. Glycolic acid is a preferred fruit acid according to this aspect of the invention. Open comedones generally require about 7 to 14 days of spot 35 therapy, while closed comedones typically require spot therapy for about 10 to 20 days in order to achieve exfoliation of the

- 10 -

horny plugs. Typically, each application of solution comprises dabbing with an applicator in an amount sufficient to wet the surface of the comedone with said solution, and the inventive therapy comprises topical applications of the  
5 solution to the comedone 2 to 3 times daily.

It will be appreciated by those skilled in the art that changes could be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not  
10 limited to the particular embodiments disclosed, but it is intended to cover modifications within the spirit and scope of the present invention as defined by the appended claims.

- 11 -

CLAIMS

1. A method for spot therapy of papulo-pustules comprising topically applying to the exterior surface of the papulo-pustule an aqueous solution containing hydrogen peroxide, said solution being applied in an amount, at a concentration and at a frequency sufficient to effect resorption of the papulo-pustule to which the solution is applied within not more than three days of therapy.

2. A method according to claim 1 wherein said solution further contains at least one of fruit acid and salicylic acid.

3. A method according to claim 2 wherein said fruit acid is selected from the group consisting of glycolic acid, citric acid, lactic acid, malic acid, pyruvic acid and combinations thereof.

4. A method according to claim 2 wherein said fruit acid is glycolic acid.

5. A method according to claim 1 wherein each application of solution comprises dabbing with an applicator in an amount sufficient to wet the surface of the papulo-pustule with said solution.

6. A method according to claim 2 wherein said therapy comprises topical applications of the solution to the papulo-pustule 2 to 3 times daily for 1 to 3 days.

7. A method according to claim 1 wherein the concentration of hydrogen peroxide in said aqueous solution is about 3 to 6 weight percent.

8. A method according to claim 2 wherein the concentration of fruit acid in said aqueous solution is an amount equivalent to about 2 to 4 weight percent glycolic acid.

9. A method according to claim 2 wherein the fruit acid is glycolic acid present in an amount of about 2 to 4 weight percent.

- 12 -

10. A method according to claim 2 wherein the concentration of salicylic acid in said aqueous solution is about 2 to 4 weight percent.

11. A method according to claim 1 wherein said papulo-pustules are lesions from conditions selected from the group consisting of adolescent acne, post-adolescent female acne, peri-menopausal acne, acne cosmetica, acne detergicans, folliculitis, and rosacea.

12. A method for reducing scars and pigmented spots from papulo-pustules of the human skin comprising topically applying to the exterior surface of the papulo-pustule an aqueous solution containing hydrogen peroxide, said solution being applied in an amount, at a concentration and at a frequency sufficient to substantially avoid hyperpigmentation and scarring after resorption of the papulo-pustule.

13. A method according to claim 12 wherein said solution further contains at least one of fruit acid and salicylic acid.

14. A method according to claim 13 wherein said fruit acid is selected from the group consisting of glycolic acid, citric acid, lactic acid, malic acid, pyruvic acid and combinations thereof.

15. A method according to claim 13 wherein said fruit acid is glycolic acid.

16. A method according to claim 12 wherein said solution is applied to the earliest papulo-pustular lesions resulting from conditions selected from the group consisting of adolescent acne, acne cosmetica, acne detergicans, folliculitis, and rosacea.

17. A method for spot therapy of comedones comprising topically applying to the exterior surface of the comedone an aqueous solution containing hydrogen peroxide, fruit acid and salicylic acid, said solution being applied in an amount, at a concentration and at a frequency sufficient to provide a comedolytic effect within about 20 days of therapy.

- 13 -

18. A method according to claim 17 wherein said fruit acid is selected from the group consisting of glycolic acid, citric acid, lactic acid, malic acid, pyruvic acid and combinations thereof.

19. A method according to claim 17 wherein said fruit acid is glycolic acid.

20. A method according to claim 17 wherein each application of solution comprises dabbing with an applicator in an amount sufficient to wet the surface of the comedone with said solution.

21. A method according to claim 17 wherein said therapy comprises topical applications of the solution to the comedone 2 to 3 times daily for about 7 to 20 days.

22. A method according to claim 17 wherein the concentration of hydrogen peroxide in said aqueous solution is about 3 to 6 weight percent.

23. A method according to claim 17 wherein said fruit acid is present in said aqueous solution at a concentration equivalent to glycolic acid in a concentration of about 2 to 4 weight percent.

24. A method according to claim 17 wherein the concentration of salicylic acid in said aqueous solution is about 2 to 4 weight percent.

25. The method according to claim 17 wherein said comedones may be open comedones or closed comedones.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US94/14536

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/74, A01N 39/00.  
US CL :424/ 78.05, 78.07, 616; 514/859

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/ 78.05, 78.07, 616; 514/859

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE, BIOSIS ONLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	US, A ,5,242,433 (SMITH ET AL.) 07 SEPTEMBER 1993, COL. 8, LINES 56-END, COL. 9, LINES 1-4, COL. 10, LINES 12-17, COL. 10, LINES 34-47.	1, 5, 11, 12, 16 ----- 2-4, 6-10, 13- 15, 17-19, 21- 25
X ---- Y	US, A, 4,557,935 (AF EKENSTAM ET AL.) 10 DECEMBER 1985, SEE ABSTRACT, COL. 3, LINES 10-17, COL. 4, EXAMPLE 1.	1, 7, 11, 12, 16 ----- 2-6, 8-10, 13- 15, 17-21, 23- 25

Further documents are listed in the continuation of Box C.  See patent family annex.

- \* Special categories of cited documents:
- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document published on or after the international filing date
- \*L\* document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*&\* document member of the same patent family

Date of the actual completion of the international search Date of mailing of the international search report

06 FEBRUARY 1995

27 MAR 1995

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Faxsimile No. (703) 305-3230

Authorized officer  
MICHAEL V. MELLER

Telephone No. (703) 308-0196

**INTERNATIONAL SEARCH REPORT**Int'l application No.  
PCT/US94/14536**C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---	US, A, 4,826,681 (JACQUET ET AL.) 02 MAY 1989, COL. 1, LINES 11-20.	1, 11, 12 -----
Y		2-10, 13-16, 17-21, 23-25
X ----	US, A, 4,428,933 (KING) 31 JANUARY 1984, COL. 1, LINES 14-20, COL. 3, LINES 52-65, AND CLAIMS 1 AND 2.	1, 11, 12, 16 -----
Y		2-10, 13-15, 17-25
Y	US, A, 4,956,184 (KROSS) 11 SEPTEMBER 1990, SEE ABSTRACT, COL. 1, LINES 1-45, COL. 3, LINES 6-10, COL. 9, LINES 37-42 AND EXAMPLE 1.	1-25